

Targeting ALDH1A1 together with nanoparticle mediated kidney specific immunotherapy delays cyst growth in ADPKD

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Introduction. ALDH1A1 is overexpressed in various cancers has also been associated with anti-tumor immunity. However, the role of ALDH1A1 and its relationship with PD-L1 in ADPKD remains elusive.

Methods. We treated *Pkd1* mutant mouse models with ALDH1A1 inhibitor DSF either alone or together with nanoparticles carried PD-L1 antibody and evaluated their effect on cyst growth, immune response and fibrosis as well as on specific PKD associated signaling pathways by immunostaining, Western blot, qRT-PCR and flow cytometry analysis.

Results. ALDH1A1 was upregulated in cyst lining epithelial cells in *Pkd1* mutant mouse kidneys. Targeting ALDH1A1 with its specific inhibitor DSF decreased cyst growth as seen by the decrease of cyst index, KW/BW ratio and BUN levels in *Pkd1*^{RC/RC} kidneys as well as cyst lining epithelial cell proliferation examined by Ki67 staining, which was mediated by the decrease of the activation of AURKA, AKT, S6 and STAT3. In addition, treatment with DSF decreased the expression of PD-L1 and activated the immune response characterized by the increase of CD8⁺ T cells and decrease the recruitment of macrophages. Our CHIP assay indicated that ALDH1A1 bound with the promoter of *PD-L1* and *Ccl2* to regulate their transcription, in which *Ccl2* is responsible for the recruitment of macrophages. Treatment with DSF induced cystic renal epithelial cell death which should be mediated by the downregulation of PD-L1 and the activation of CD8⁺ T cells in *Pkd1*^{RC/RC} kidneys. Treatment with DSF and the mesoporous silica nanoparticles (MSN) conjugated with PD-L1 and kidney specific cadherin-16 (CDH16) antibodies has synergized effect on cyst growth.

Conclusions. ALDH1A1 is a novel transcription factor binding on the promoters of specific genes, such as *PD-L1*, *CCL2* and fibrotic genes. Targeting ALDH1A1 with its inhibitor either alone or in combination with nanoparticles mediated PD-L1 antibody is a novel therapeutic strategy for ADPKD.

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